An emerging platform for drug delivery: Aerogel based systems

Zeynep Ulker, Can Erkey *
Department of Chemical and Biological Engineering, Koc University, 34450 Sarıyer, İstanbul, Turkey

Abstract

Over the past few decades, advances in "aerogel science" have provoked an increasing interest for these materials in pharmaceutical sciences for drug delivery applications. Because of their high surface areas, high porosities and open pore structures which can be tuned and controlled by manipulation of synthesis conditions, nanostructured aerogels represent a promising class of materials for delivery of various drugs as well as enzymes and proteins. Along with biocompatible inorganic aerogels and biodegradable organic aerogels, more complex systems such as surface functionalized aerogels, composite aerogels and layered aerogels have also been under development and possess huge potential. Emphasis is given to the details of the aerogel synthesis and drug loading methods as well as the influence of synthesis parameters and loading methods on the adsorption and release of the drugs. Owing to their ability to increase the bioavailability of low solubility drugs, to improve both their stability and their release kinetics, there are an increasing number of research articles concerning aerogels in different drug delivery applications. This review presents an up to date overview of the advances in all kinds of aerogel based drug delivery systems which are currently under investigation.

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1. Introduction

Over the past few decades, research efforts were mainly directed to understand the physicochemical properties of drug molecules as well as the mechanisms of cellular uptake to achieve effective therapeutic strategies [1]. However, the treatment of some diseases like cancer involves the use of some toxic drugs which have adverse side effects and limited effectiveness because they lack target specificity [1]. Furthermore, both pathological processes occurring in the body and the body's response to different kinds of drugs can alter the expected therapeutic effect even though the required dose of the drug for a specific disease is already known. Thus, the needed amount of the drug can be different from the one which is administered.

Controlled release systems are being developed to deliver the needed amount of drug, to increase the effect of the drug in the body, to protect it from physiological degradation, to improve patient comfort and to be able to control the location where the drug is actually delivered [2]. These systems are being used to achieve a spatial and time dependent control of delivery. Additionally, economic considerations related to the reduction in the frequency and the dose of the drug and the extension of the product life are the key factors behind research efforts in this field [3].

Drug delivery systems are difficult to design as there exist various mechanisms which are involved in the release processes of drugs [2].
Various factors such as the degree of absorption of the drug or the diffusion limitations of the drug in the medium need to be considered for effective treatment. Recently, the use of nanotechnology in drug delivery has attracted a lot of interest due to its potential for development of systems that are site specific and/or that offer time dependent controlled delivery [4]. Nanoparticles, nanocapsules or micelles as nanotechnology based drug delivery systems offer many advantages over the conventional delivery systems. Furthermore, the problems associated with the delivery of a free drug such as poor solubility, tissue damage on extravasation, rapid breakdown in vivo associated with the delivery of a free drug such as poor solubility, tissue over the conventional delivery systems. Furthermore, the problems nanotechnology based drug delivery systems offer many advantages controlled delivery [4]. Nanoparticles, nanocapsules or micelles as Table 1 management of systems that are site specific for effective treatment. Recently, the use of nanotechnology in drug delivery has attracted a lot of interest due to its potential for development of systems that are site specific and/or that offer time dependent controlled delivery [4]. Nanoparticles, nanocapsules or micelles as nanotechnology based drug delivery systems offer many advantages over the conventional delivery systems. Furthermore, the problems associated with the delivery of a free drug such as poor solubility, tissue damage on extravasation, rapid breakdown in vivo, unfavorable pharmacokinetics, poor biodistribution, and lack of selectivity for target tissues can be overcome by designing drug delivery vehicles via nanotechnology [2,5]. The physicochemical properties of these nanostructured drug delivery systems are adjusted either based on the drug type or the delivery route such as nasal, transdermal or oral.

Porous materials are important components of drug delivery vehicles for the encapsulation of a variety of molecules due to their large inner surface areas, high surface to volume ratios, large pore volumes and uniform pore sizes [6–8]. Based on the International Union of Pure and Applied Chemistry (IUPAC) classification, the pores of the solids are distinguished according to size: pore sizes smaller than 2 nm represent micropores, those in the range of 2 nm to 50 nm are called mesopores and those above 50 nm are denoted as macropores. The effectiveness of these porous materials for various applications such as adsorption, separation or catalysis depends on the size, shape and volume of these pores [9]. A wide variety of micro- and mesoporous systems and the effects of their pore and surface properties on drug loading, release or matrix–drug interactions are already under investigation for sustained or controlled release applications [6,7,10,11].

Aerogels as the lowest density solids with very high porosities and demonstrated biocompatibilities are attracting increased attention as components of drug delivery vehicles as evident from the increasing number of research articles and thesis studies [12–15]. Aerogels were first synthesized in 1931 by Samuel Kistler who defined them as the materials keeping their pore and network structure intact upon exchanging their pore liquid with gas [16]. The unique properties of these highly porous materials with open pores and high surface areas are attributed to their irregular solid structure which can be tuned through the proper selection of the preparation conditions.

Since the 1960s, silica aerogels have been used as additives for consumer products such as toothpastes or cosmetics [15]. About 60 years after their discovery by Kistler, organic aerogels were proposed for use in medical applications as diagnostic agents and artificial tissues, and specifically in drug delivery systems [17]. Since then, there has been an increasing interest for the use of inorganic or organic aerogels in the area of drug delivery.

2. Synthesis of aerogels

Sol–gel polymerization is the commonly employed method for the preparation of inorganic aerogels as shown in Fig. 1 [15,18–20]. Metal alkoxides such as tetraethylorthosilicate (TEOS) or tetramethylorthosilicate (TMOS) are the generally used chemical precursors for the synthesis of silica aerogels (Table 1). First, these precursors are hydrolyzed in a mixture of water and alcohol where the alkoxide groups of the precursor are replaced with hydroxyl groups as shown in Eq. (1).

\[
\text{Si(OR)}_4 + 4\text{H}_2\text{O} \rightarrow \text{Si(OH)}_4 + 4R - \text{OH}
\]  

(1)

<table>
<thead>
<tr>
<th>Aerogel type</th>
<th>Precursor</th>
<th>Catalyst or crosslinker</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silica aerogel</td>
<td>Tetraethylorthosilicate, Tetraethylorthosilicate, triethoxysilane, methytrimethoxysilane, sodium metasilicate and related salts, methyl silicate 51, polyethoxysiloxane, silbond H-5</td>
<td>HCl, H,HSO4, HF, NH4OH</td>
<td>Alcohols, acetone, ethyl acetonate</td>
</tr>
<tr>
<td>Titanium aerogel</td>
<td>Tetraethyl orthotitanate, titanium n-butoxide, titanium tetraisopropoxide</td>
<td>HNO3, Divalent or multivalent cations and glucono-δ-lactone</td>
<td>Ethanol, methanol tetrahydrofurane</td>
</tr>
<tr>
<td>Alginate aerogel</td>
<td>Alginate acid sodium salt</td>
<td></td>
<td>Distilled water</td>
</tr>
<tr>
<td>Starch aerogel</td>
<td>Potato starch, high amylose maize starch, corn starch</td>
<td>Epichlorohydrine, NaOH</td>
<td>Distilled water</td>
</tr>
<tr>
<td>Cellulose aerogel</td>
<td>Plant cellulose, bacterial cellulose</td>
<td></td>
<td>Calcium thiocyanate, NaOH-water solution or ionic liquids</td>
</tr>
<tr>
<td>Whey based aerogel</td>
<td>Whey protein isolate</td>
<td>HCl, NaOH</td>
<td>Distilled water</td>
</tr>
</tbody>
</table>

Fig. 1. The scheme of the sol–gel polymerization method (circles represent nanoparticles of solid component which form the 3-D network).
The kinetics of hydrolysis reaction can be accelerated by the addition of an acid or a base catalyst. Subsequently, Si(OH)$_4$ molecules go through water (Eq. (2)) and alcohol (Eq. (3)) condensation reactions forming a silica network. This step can be accelerated by the addition of a base catalyst.

\[
\text{Si} - \text{OH} + \text{HO} - \text{Si} \rightarrow \text{Si} - \text{O} - \text{Si} \rightarrow + \text{H}_2\text{O} \quad (2)
\]

\[
\text{Si} - \text{OR} + \text{HO} - \text{Si} \rightarrow \text{Si} - \text{O} - \text{Si} \rightarrow + \text{R} - \text{OH} \quad (3)
\]

The mixture finally forms a gel which is mostly constituted of SiO$_2$. However, some side chains might remain unreacted (Si – OR) or partially reacted (Si – OH) at the end of the condensation reactions. These Si – OH groups render the aerogel hydrophilic and make it susceptible to water adsorption leading to structural collapse. To improve the mechanical strength of these wet gels and to finish hydrolysis and condensation reactions of unreacted precursors in the gels, they are placed in an aging solution consisting of water and alcohol. This step is necessary to obtain more compact structures which are more resistant to shrinkage and any damage. Then, the gel is subjected to solvent exchange step during which it is placed in pure solvent which is generally an alcohol to replace water and to remove any impurities remaining in the pores.

The final step is to dry this wet gel which is also called alcogel without damaging its structure. The wet gels which are dried under ambient conditions cannot withstand the capillary stresses and fracture during the drying process. Therefore, alcogels are dried using a process called supercritical extraction. Supercritical CO$_2$ (scCO$_2$) is able to dissolve and extract the pore liquid and reduce the capillary pressure created within the pores due to its low surface tension. Alcogels which are dried supercritically are called aerogels whereas the ones which are dried at ambient pressure are denoted as xerogels. Supercritical drying is carried out at pressures around 100 bars and thus requires equipment resistant to shrinkage and any damage. Then, the gel is subjected to solvent exchange step during which it is placed in pure solvent which is generally an alcohol to replace water and to remove any impurities remaining in the pores.

Aerogels can be synthesized in any form depending on the shape of the mold in which gelation takes place. The choice of the material of the mold is equally important as the preparation conditions in order to obtain a crack-free monolithic aerogel. It should be chosen so that the mold would not stick to the alcogel surface allowing easy release, and also should not interact with the sol before and after the gelation. Poco described a technique about how to obtain low density monolithic aerogels [25] are also prepared using the same sol–gel route but with different precursors.

Organic aerogels mainly polysaccharide based ones like starch aerogels, alginate aerogels and cellulose aerogels which are promising for drug delivery applications are also synthesized in a similar manner to inorganic silica aerogels [26]. The primary step is to form a hydrogel from an aqueous starting solution triggered by a cross-linking promoter which can have either a chemical nature (chemical cross-linker) or physical nature (pH, temperature) [26]. The subsequent step which is called the aging/solvent exchange step involves the replacement of the water within the porous structure with an appropriate solvent which is usually an alcohol. The next and final step is to dry the wet gel supercritically with carbon dioxide. Although their surface areas are usually smaller than those of silica aerogels, organic aerogels have still reasonably high surface areas for drug delivery applications.

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Aerogels cannot only be synthesized in monolithic form but also in the form of granules, or beads as shown in Fig. 2 which increases their usability in various applications in the drug delivery field requiring different sizes and shapes. A simple mechanical grading can be used for the production of aerogel granules or powders. Because of their continuous network, the pore and surface properties of aerogels do not change during this mechanical grading which therefore is a powerful and simple tool for the preparation of smaller size aerogel particles. Aerogels which are produced by ambient pressure drying are generally

![Fig. 2. Calcium alginate aerogel samples in different forms: a) monoliths, b–c) particles. Reprinted from [26] with permission from Elsevier.](image-url)
More research effort should be similarly given to better analyze the solutions with different concentrations and changing aging times have reducing the distance between the particles. Meanwhile, using aging er pore volume [34] which may be due to a more compact network reaction kinetics, the nature of the solvent, and the molar ratios of Section 5on using organic aerogels as drug delivery systems. Adapted from [15].

in powder form. For example, Joung et al. synthesized aerogel powder via ambient pressure drying at atmospheric pressure and under vacuum at 0.08 or 0.12 atm [28]. The authors claimed that avoiding the supercritical drying step shortened the total time of the process which consisted of dissolving a water glass solution and hexamethyldisilazane (HMDS) in an organic solvent prior to gelation which was triggered by the addition of an inorganic acid to the solution. After solvent exchange, the silica hydrogel was dried and silica aerogel powders were obtained.

Such aerogel powders can be easily incorporated into already existing pharmaceutical formulations after they are loaded with drugs. Recently, the tabletting properties of silica aerogels along with different silicates were investigated for their suitability as carriers for liquids or solid amorphous drugs [29]. The tabletability of the silica aerogel was found to be better than that of Aerosil® 200 (colloidal silica) but worse than that of Neusilin® (synthetic amorphous form of magnesium alumino-metasilicate) and Florite® (calcium silicate). The hardness of the tablets obtained by the compaction of plain silica aerogels was found to be in an acceptable range.

Emulsion polymerization is another technique which can be used for the synthesis of spherical aerogel particles [30–32]. This method involves the preparation of an emulsion by mixing the sol with a suitable oil (a water in oil emulsion) followed by gelation of the dispersed phase. Surfactants are also sometimes added to the emulsion at different concentrations. After separation of microspheres from the oil phase, supercritical drying is used to obtain the aerogel microspheres which can be either inorganic or organic. Alternatively, alginate aerogel microspheres were prepared via egg-box gelation technique [33]. Dropwise addition of the polycosaccharide solution into a solution containing ions which triggered gelation, resulted in the immediate formation of spherical gels. The details of this synthesis technique are given in Section 5 on using organic aerogels as drug delivery systems.

The possibility of controlling the nanostructure of these materials is another intriguing property. The choice of the catalyst affecting the reaction kinetics, the nature of the solvent, and the molar ratios of the reactants are some of the important parameters to control this nanostructure. Saqging et al. have shown that increasing the organic precursor to water ratio in the sol to synthesize resorcinol formaldehyde aerogels has resulted in a reduction in the average pore size and a smaller pore volume [34] which may be due to a more compact network reducing the distance between the particles. Meanwhile, using aging solutions with different concentrations and changing aging time have been shown to change the porosity characteristics of aerogels [35]. More research effort should be similarly given to better analyze the effect of synthesis conditions on the porous structure of the aerogels.

3. Preparation of aerogel based drug delivery systems

Drug delivery vehicles based on aerogels can be prepared by different methods such as the addition of the drug during the conventional sol–gel process or during the post treatment of the synthesized aerogels as shown in Fig. 3 [15]. During the sol–gel procedure, the drug can be loaded either before the gelation or during the aging steps. The addition of the drug before the gelation is an appealing way due to its simplicity and flexibility for different target compounds. With this approach, the drug molecules which are dissolved in the initial solution are expected to be trapped in the aerogel network during the gelation. Subsequent aging, solvent exchange and drying steps lead to the drug loaded aerogel.

The other approach is the addition of the therapeutic agent during the aging step. The alcolgel is contacted with an aging solution which contains the drug which then diffuses into the pores of the aerogel from the aging solution. This process might require a long time depending on the diffusion rate of the drug molecules into the pores of the aerogels. The diffusion rate depends on the size of the molecules, the size of the pores and the initial concentration of the aging solution. The diffusion continues until the concentrations in the pore liquid and the aging solution become equal. Subsequently, the alcolgel containing the drug is subjected to supercritical drying. During this stage, scCO2 also acts like an anti–solvent reducing the solvent power of the solvent which is present in the pores. As more and more CO2 is dissolved in the solvent, the drug starts to precipitate in the pores of the alcolgel.

This process continues until all of the solvent inside the pores is removed. Subsequently, the system is depressurized to obtain the drug loaded aerogel. The solvent should be selected such that the drug should be soluble in the solvent, the solvent should not damage the aerogel and the solvent should be extractable using scCO2.

This process is very similar to the gas anti solvent (GAS) process in which an anti-solvent is added to a binary solution of a solute in a solvent to initiate a phase separation due to a decrease in the solubility of the solute [36]. The chosen antisolvent has no or little affinity for the solute but forms at least a partially miscible solution with the solvent [37]. ScCO2 is one of the most widely investigated anti solvents. The crystallization of various drugs like paracetamol [38], griseofulvin [39] and copper indomethacin [40] via GAS process has been investigated. The crystallization thermodynamics of these drugs on aerogels during supercritical drying stage should be similar to the thermodynamics of conventional GAS process. The only difference is the fact that the process occurs inside nano-sized pores. In order to control the drug loading process using this technique, a detailed knowledge of the ternary phase behavior of the system consisting of the alcohol (the solvent), the drug (the solute) and the CO2 (the anti-solvent) should be known in advance as shown in Fig. 4.

As shown in the diagram for a mixture above its critical pressure, the solute forms a partially miscible mixture with the solvent and scCO2 whereas the solvent forms a miscible mixture with scCO2. The process starts with a liquid solution at a certain solute concentration. As the concentration of anti-solvent CO2 increases inside the liquid phase, it causes a volumetric expansion of the system reducing the bulk density of the solution which in turn lowers the solvating power of the solvent [38]. Thus, the mixture passes from the homogeneous liquid (L) phase to a two phase solid–liquid (S–L) and the solute starts precipitating. The path then passes through a solid–vapor (S–V) region with an increasing amount of solid phase due to the decreasing amount of liquid through its extraction to scCO2 [37]. The solid may be in amorphous form or crystal form depending not only on the process parameters such as pressure, temperature and depressurization rate but also on the interaction of the aerogel matrix with the drug molecules. Strong adsorption favors amorphous precipitates whereas weak interactions result in crystal formation [41]. The structure of the resulting drug particles is important for the kinetics of drug release. These processes require the drug to be insoluble in scCO2 to prevent the drug from being removed from the aerogel matrix during supercritical drying with CO2.

![Preparation routes of drug loaded aerogels](image-url)
Furthermore, the reactivity of the drug with the constituents of the sol which could in turn affect the gelation process or the final properties of the product and the stability of the drug in the matrix should as well be deeply investigated for these loading methods.

Second approach for loading the drug to the aerogel involves contacting the pure aerogel with a solution of the drug after the supercritical drying step similar to the study involving the liquid adsorption of a basic dye on silica aerogels [42]. The drug would then diffuse into the pores of the aerogel and would adsorb on the surface of the aerogel. Subsequent removal of the solvent would then lead to a drug loaded aerogel. However, this process has drawbacks for various aerogels such as silica aerogels since they are hydrophilic by nature due to their surface hydroxyl groups and rapidly collapse when immersed in liquid solutions. Therefore, a possible solution is to load the drug from the supercritical phase. However, this method requires the drug to be soluble in scCO2. For such CO2 soluble drugs, the loading capacity depends both on their solubility in scCO2 and on their affinity to the aerogel surface. Thus, the structural properties of the aerogel as well as its surface properties affect the loading capacity [15]. Another advantage of using scCO2 is that it is non toxic and is easily removed from the product only by lowering the pressure leaving no residue on the treated medium. In a pioneering study, Smirnova et al. demonstrated that aerogels can be loaded with pharmaceutical compounds by adsorption from their solutions in scCO2 [43]. In this regard, it is crucial to know the thermodynamics and kinetics of adsorption of drugs for the design of such processes and to control loadings. The thermodynamics of adsorption is generally described by adsorption isotherms. The adsorption isotherms of various drugs in supercritical CO2-aerogel systems were measured in various studies [44–46]. The adsorption isotherms of most of the drugs could be represented by the Langmuir isotherm showing that the loading of the drug can be increased until the saturation point of the matrix. The findings in the literature on the adsorption of metal complexes on different types of aerogels can also be beneficial in guiding future studies in this field [47,48]. The kinetics of adsorption depends on a series of complex mass transfer processes such as diffusion inside the pore volume, external mass transfer and surface diffusion. Zhang et al. developed a mass transfer model based on diffusion inside the pore volume to describe the kinetics of adsorption of an organometallic compound onto carbon aerogels from supercritical solutions [47]. The same model was also applied to successfully predict the kinetics of adsorption of a platinum precursor onto resorcinol formaldehyde aerogel spheres [48]. Adsorption isotherms were represented by a modified Langmuir model and it was shown that the measured and the modeled adsorption kinetics of the platinum precursor were in good agreement. A similar model could as well be used in order to describe the adsorption kinetics of various drugs on porous aerogels. However, determination of some important parameters such as tortuosity not by regression from experimental data but from other sources would be beneficial.

If the solubility of the chosen drug in scCO2 is low, then the adsorbed amount may not reach the saturation level but remains low. The solubility of various drugs such as ketoprofen, nimesulide, piroxicam [49], aspirin [50], some fat soluble vitamins [51] and many others [37] in scCO2 can be found in the literature. The solubility of the drug is not only dependent on its chemical structure but also on the pressure and the temperature of the system which are directly related to the density of the supercritical phase. Increasing density of the supercritical phase increases the solubility due to enhanced molecular interactions at higher densities [37]. The solvent power of CO2 at lower pressures can also be increased by the addition of an entrainer to the system due to additional interactions between the drug and the entrainer [52]. However, an additional component complicates the adsorption thermodynamics and necessitates further measurements for the new ternary system and there are no such studies in the literature. Thus, more research should be devoted to understand the phase behavior of drug-solvent-supercritical fluid mixtures and adsorption from such solutions on various aerogels.

A summary of the studies on aerogel based drug delivery systems is given in Table 2 indicating the type of the aerogel, the drug and the loading method which is used in each study.

4. Inorganic aerogel based drug delivery systems

4.1. Native silica aerogels

Among the various materials that have been investigated for drug delivery, silica based materials were shown to be biocompatible [1]. Furthermore, these materials and their functionalized forms were shown to enable the controlled release of various therapeutic agents [1,3,68,69].

The chemical structure of silica aerogels resembles fumed silicon dioxide which has been in use in the pharmaceutical industry for many years. The so-called product “Aerosil” was developed by a German company called Degussa and has been in the market since 1940. The clinical tests showed that this product was not harmful to the human body [70]. Orally administered Aerosil was shown to pass through the gastrointestinal tract without being resorbed in detectable quantities [15]. Silica aerogel, having the same chemical structure as Aerosil is expected to have similar clinical characteristics. Silica aerogel presents even superior characteristics due to its larger surface area (around 1000 m²/g compared to around 200 m²/g) and its tunable properties [15].

Various patents and studies concerning the use of silica aerogels as drug delivery systems can be found in the literature [43,71]. In 2001, Schwertfeger et al. reported that silica aerogels are promising materials as carrier matrices and utilized both hydrophilic and hydrophobic aerogels as drug delivery systems [71]. The corresponding aerogels were primarily loaded with several pharmaceutically active compounds such as furosemide-sodium, penbutulol hemisulfate, and methylprednisolone by adsorption from a solution of the drug until equilibrium was reached and then filtered and dried to obtain drug loaded aerogels. The final material was in powder form. Since the loading was carried out from a liquid phase after drying, some reduction in pore volume must have occurred. Nevertheless, they demonstrated that hydrophobic drugs can be incorporated into a hydrophilic aerogel and hydrophilic drugs into a hydrophobic aerogel [71].

Drug release studies have shown that high drug loadings could be achieved by using aerogels as carrier systems and it was demonstrated that the drugs adsorbed on hydrophilic silica aerogels dissolved faster than the crystalline form of the corresponding drugs [45,46,54,55].
Thus, hydrophilic aerogels were proposed for use in immediate release systems as an alternative to systems prepared by conventional micronization techniques [45]. This fast release was related to the increased surface area of the drug which was adsorbed on the silica aerogel and the disintegration of the hydrophilic aerogels when immersed in aqueous solutions. As the adsorbed drugs were no more in their crystalline form, no energy was required to destroy their crystal lattice leading to a faster dissolution [45]. Thus, the open pore structure of the hydrophilic silica aerogels allowing fast penetration of liquids inside and thereby collapsing their structure makes hydrophilic aerogels unsuitable for prolonged release but suitable for immediate release applications especially for poorly water soluble or hydrophobic drugs.

Smirnova et al. loaded hydrophilic aerogels with two model drugs which were griseofulvin and ketoprofen by adsorption from scCO\textsubscript{2} [45]. It was shown that maximum loading of the drug depended on the chemical structure of the drug because of the different adsorption isotherms for the two drugs. The release rates of the drugs were five and four times higher than their crystalline forms for ketoprofen and griseofulvin, respectively. The release rate was found to be independent of the density of the hydrophilic silica aerogel since the collapse of the matrix was the key factor governing the rate. Guenther et al. utilized drug loaded hydrophilic silica aerogels as dermal drug delivery systems [54]. It was shown that the release and the penetration properties of the model drug, dithranol, were improved when it was released from the aerogel matrix. The adsorption of dithranol on silica aerogels resulted in higher flux and shorter lag times in the penetration of dithranol in two different artificial membranes and human stratum corneum compared to the suspension of the crystalline form of dithranol. Caputo et al. recently showed that the release rate of another drug, nimesulide, was also increased upon loading on hydrophilic silica aerogels by adsorption from scCO\textsubscript{2} [59]. Around 80% of nimesulide was released within the first few minutes compared to the dissolution of native crystalline drug which took about 2 h. The kinetics of adsorption was also investigated by measuring the uptake amount of nimesulide on silica aerogels at different times. The slow adsorption kinetics was related to the low affinity of the nimesulide towards the silica aerogel and also to its low solubility in scCO\textsubscript{2}. A subsequent study by the same group on nimesulide adsorption on silica aerogels involved the use of an entrainer to increase the solubility of the drug in scCO\textsubscript{2} [58]. It was shown that the uptake was six times higher when ethanol was used as the entrainer.

Along with increasing the bioavailability of low solubility drugs, the aerogel matrix has also been shown to prolong the stability of the drug. In the study of Murillo-Crenaeas et al., a model drug triflusal was loaded on silica aerogel monoliths and on polymethylmethacrylate (PMMA) for comparison [56]. Triflusal which was dispersed in the aerogel matrix by adsorption from the supercritical phase was relatively stable under ambient conditions up to 6 months. When it was loaded on PMMA and stored under the same conditions, it was gradually changed to 2-hydroxy-4-trifluoromethyl benzoic acid (HTB metabolite) which is the product of progressive hydrolysis of triflusal in water. It was suggested that the acidity provided by the aerogel matrix to the adsorbed water stabilized triflusal molecules against hydrolysis. Furthermore, it was observed that the aerogel systems exhibited a much faster release rate and 80% of the drug was released within the first few minutes.

Besides silica aerogels, there exist other inorganic aerogels like titania based aerogels. Moreover, surface functionalized titania nanoparticles with flavin mononucleotide as a fluorescent probe for intracellular imaging were also loaded with chemotherapeutic drugs such as doxorubicin for drug delivery applications [72]. To test the potential of these materials in intracellular applications, safety and toxicological tests were also conducted. It was shown that these mesoporous nanoparticles with high surface areas such as 237 m\textsuperscript{2}/g were also biocompatible. Thus, studies on the suitability of titania based aerogels with higher surface areas and porous structures for drug delivery applications would be worthwhile.

### 4.2. Surface functionalized aerogels

For hydrophilic aerogels, the limitation of fast matrix erosion when placed in liquids can be overcome by replacing the surface hydroxyl groups with hydrophobic groups. Such a surface treatment procedure makes the aerogel matrix hydrophobic limiting the penetration of liquid water into the pores. Thereby, the burst release of drugs could be hindered and a controlled release could be achieved. This replacement could be achieved by several methods. One approach is to use different silica precursors in the synthesis. Using different organosilanes such as methyltrimethoxysilane (MTMS), methyltriethoxysilane (MTE), dimethyldichlorosilane (DMCS), trimethyloxysilane (TMES), ethyltriethoxysilane (ETES) and phenyltriethoxysilane (PTES) as co-precursors, aerogels with different hydrophobicities can be obtained due to the reaction of the silyl groups of the co-precursors with the silica network during the condensation reactions [73]. Synthesizing aerogels using directly MTMS as the precursor resulted in superhydrophobic aerogels with contact angles as high as 173° [74].

Surface modification of the aerogels can also be performed after the drying step. Since contacting the aerogels with liquid solutions containing surface modification agents disintegrates the aerogels, treatments from either vapor phase or supercritical phase can be applied. For example, the hydrophilic surface of a silica aerogel was modified...
via reaction with gaseous methanol for 10 h [75]. The treatment led to extremely hydrophobic aerogels which could even float on water without getting wet for several hours [44]. Besides methanol, hexamethyldisilazane (HMDS) can also be used as a surface modification agent either in pure vapor form or as a solution in scCO₂ as shown in Fig. 5 [76]. Aerogels with a contact angle as high as 130° could be obtained using HMDS dissolved in scCO₂. The phase behavior of HMDS and CO₂ at high pressures was recently investigated by measuring the bubble point pressures for different compositions at different temperatures and it was found that HMDS and CO₂ forms miscible mixtures at all compositions at relatively low pressures [76]. Such data are necessary to design and develop large scale processes to modify the surfaces of aerogels.

Although hydrophobization of the surface of the aerogel matrix can retard the collapse of the aerogel matrix and thus enable prolonged release, the modification of surface hydroxyl groups which are known as active adsorption sites might decrease the adsorption capacity of the same aerogels [15]. Therefore, a larger quantity of aerogel would be needed to load the same amount of pharmaceutical compound compared to non-functionalized aerogels. The effect of surface chemistry on loading capacity was also demonstrated by Bozbag et al. in a study on the adsorption of a copper complex (CuDI6) onto different types of aerogels such as silica aerogel, resorcinol formaldehyde aerogels and carbon aerogels [77]. The adsorption capacity of the silica aerogels was found to be lower than that of the carbon and resorcinol formaldehyde aerogels as shown in Fig. 6 due to the hydrophilic nature of their surface although they have greater surface area.

Hydrophobic silica aerogels were synthesized and tested for controlled release applications and their release behavior was compared with that of hydrophobic aerogels [55,57]. Moreover, it was also shown that the adsorption and release rates could be controlled by the density and the hydrophobicity of the aerogels. As shown in Fig. 7, the loading of the ketoprofen on hydrophilic aerogels was greater compared to hydrophobic ones at all densities. Furthermore, the loading increased with increasing aerogel density since aerogels with higher densities had higher surface areas [57].

In another study which compared hydrophilic and hydrophobic silica aerogels as drug delivery vehicles, it was again suggested that the reduction in the available effective surface area due to less OH sites had resulted in lower drug loading amounts for the hydrophobic aerogels [57]. Furthermore, hydrophobic aerogels were shown to be suitable for the prolonged release of drugs since their release mechanism is governed by diffusion rather than collapse of the network integrity. The burst release of the drug which was adsorbed on the surface was followed by its slow diffusion from the pores which allowed control over the release to some extent as shown in Fig. 8. Thus, it was concluded that the release kinetics could be controlled by changing the hydrophobicity and the density of the aerogels [57].

The surface of the silica aerogels can also be modified with amine groups which can be incorporated from either gas phase or liquid phase [67]. To functionalize from the liquid phase, the wet gel can either be prepared with 3-(aminopropyl)-trimethoxysilane (APTMS) as the catalyst or it can be placed in an aging solution containing APTMS. For the gas phase functionalization, the pure aerogel can be contacted with the vapor of APTMS solution. Functionalization from the gas phase was found to preserve the pore properties of the native aerogel; however, the concentration of the surface amino groups was found to be lower compared to that in liquid phase modification. Overall, the drug loading capacity was increased using both methods owing to the strong interactions of amino groups with acidic groups of the model drug, ketoprofen. Moreover, the amino functionalization did not retard the release rate of ketoprofen. As the functionalized aerogels were also hydrophilic, the release was also thought to be dependent on the collapse of the aerogel matrix. It was shown that 70% of the

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**Fig. 5.** Surface functionalization with HMDS.

**Fig. 6.** Adsorption isotherms of CuDI6-CO₂-aerogel systems at 10.6 MPa and 35 °C [78].

**Fig. 7.** The loading of ketoprofen on silica aerogels with different densities. Reprinted from [55] with permission from Elsevier.

**Fig. 8.** The release of ketoprofen from hydrophilic and hydrophobic aerogels with different densities in 0.1 N HCl at 37 °C. Reprinted from [55] with permission from Elsevier.
adsorbed drug was released within the first 30 min for all formulations used in the study.

4.3. Silica aerogels for the encapsulation of biomolecules

Protein drugs are increasingly becoming key components of modern medical care. Four of the top fifteen U.S. pharmaceutical products by sales in 2008 were protein drugs [79]. The studies which demonstrated the potential of aerogels for drug delivery suggest the suitability of these porous materials for the encapsulation of protein or enzymes [15].

An enzyme within a host material (a supported enzyme) is more desirable than free enzymes for various applications such as biocatalysis since it is easier to remove the supported enzyme from the reaction media and separate it from the reaction products [80]. However, the encapsulation should affect neither the stability nor the activity of the enzyme. Sol–gel techniques were used to encapsulate various enzymes [81] and it was shown that enzymes usually retained their catalytic activity and were protected from degradation within their silica cages. Due to a porous structure enabling the spreading of the enzyme on a large surface area, silica aerogels were shown to be suitable hosts for the encapsulation of various biomolecules such as enzymes or proteins without deteriorating their properties [80,82,83]. For example, the biocatalytic activity of an aerogel encapsulated lipase for trans-terification reactions was studied [83]. It was shown that the enzyme was well dispersed in the aerogel matrix which prevented its agglomeration. Moreover, the catalytic activity of the lipase was higher in supercritically dried aerogels compared to ambient pressure dried aerogels [80] which was attributed to the highly porous structure of the aerogel which enabled the enzyme to be flexible in its host matrix. For instance, the specific pore volumes of the synthesized aerogels were shown to be around 2 cm³/g compared to aerogels with 0.5 cm³/g giving a higher area for the enzymes to be more flexible. Recently, it was also shown that a protein, cytochrome c could be trapped in an aerogel matrix using a nanogluing approach [84,85]. Proteins were added together with silver or gold nanoparticles to the sol just before the gelation leading to the spontaneous formation of loosely multilayered superstructures of proteins. The use of supercritical drying then resulted in protein–noble metal–aerogel composites. These protein–metal superstructures displayed rapid gas phase recognition of nitric oxide while entrapped in the aerogel network and remained active for weeks at room temperature [84]. Since not all proteins might be able to form superstructures with metal nanoparticles, the researchers also investigated the stability of the same protein, cytochrome c, in the aerogel matrix without nanogluing it to a noble metal [85]. Although the superstructure was found to be only slightly more stable than the protein alone, it was revealed that proteins preserved most of their structural integrity and responded to nitric oxide without the presence of metal nanoparticles. These studies indicate the potential of the encapsulation of proteins within aerogel matrices which could also serve as a basis for the development of aerogels as protein delivery vehicles.

4.4. Composite aerogels

Composite materials are always attractive due to the combination of diverse functionalities in one entity. It is thereby possible to suppress the disadvantages of one material with superior properties of another. Thus, in the pharmaceutical field, composite aerogels might be an alternative choice as drug delivery vehicles. Polyurea is promising candidates as secondary materials since there are a variety of polymers which are already used in the medical field. The addition of polymer into the aerogel matrix may improve the mechanical properties of the overall composite retarding its collapse and thereby prolonging the drug release. It may also be possible to replace supercritical drying by air drying if the network has sufficient strength. In addition, any change in surface properties could favor the adsorption of some drugs by increasing the interaction between the drug and the surface of the aerogel matrix. The organic entity can also interfere with the network formation with possible formation of macro or micropores due to settlement of the organic part into different locations. The presence of diverse sized pores could enable the loading of different sized drugs.

Several methods have been already developed to synthesize silica aerogel polymer composites for a wide variety of applications other than drug delivery. Co-condensation reactions with organically substituted precursor or polymers [86], attachment of styrene [87], isocyanates [88,89] or epoxides [90] to the modified amine ends of the aerogel surface or liquid phase modifications without using any additional substrate but with direct addition of the monomer in the initial solution [91,92] are some methods which were used for preparation of the composites. Supercritical fluid deposition and chemical vapor deposition [93–95] have also been attracting increased attention as past synthesis modification techniques. Although the materials prepared in these studies were not intended for use in drug delivery applications, the same preparation techniques can in principle be used to obtain suitable materials for pharmaceutical applications.

Sabri et al. investigated the short and long term biocompatibility of polyurea crosslinked silica aerogel composite implants in a Sprague-Dawley rat model [96]. The tissues surrounding the implants or the distant organs did not show any noticeable systemic reaction or immune response. Although this study was carried out with a small number of animals, the results suggest that these polyurea based silica aerogels could be useful as drug delivery vehicles. It was suggested that the nanoporous and three dimensional surface structure of the aerogel limited and prevented its movement by forming anchoring sites with nearby tissues eliminating the need for sutures and thus increasing patient comfort. In vivo experiments suggested that further investigations should be carried out to better understand the interaction between the aerogel implant and the living tissue.

In a recent article, a composite of silica aerogel with a metal organic framework (MOF) was synthesized via sol–gel route [97]. Various studies concerning the biomedical applications of MOFs are encouraging for the future use of these materials in the medical field [98,99]. Thus, similar composites could be prepared with a variety of MOFs and BIOMOFs which are already under consideration as promising candidates for drug delivery and drug storage applications. The combination of two materials with high surface areas and different surface properties could be very interesting for maximizing the drug loading capacity of the delivery systems. It seems that there is a lot to explore in this field which may lead to the development of superior devices.

5. Organic aerogel based drug delivery systems

Even though silica aerogels have interesting and unique properties, they are not biodegradable which may complicate in vivo applications and limit their use for some drug delivery applications. As it was already shown that controlled drug release kinetics and biomolecule entrapment while maintaining its biological functionality can be achieved with these aerogels, more research should be devoted to this area in order to determine how these aerogels can be applied to various biological systems. Alternatively, organic aerogels mostly based on polysaccharides possess several beneficial characteristics of inorganic aerogels such as high surface areas and porous structures and they are also biodegradable. Meanwhile, the biodegradability of these organic aerogels should also be investigated in vivo case by case.

Several patents have been already published claiming that organic aerogels could be loaded with pharmaceutical compounds. In 1995, Berge et al. have shown that resorcinol formaldehyde aerogels could be loaded with testosterone adipate and 5-fluorouracil via the aforementioned methods in Section 3 [17]. Lee et al. loaded organic aerogels based on transacylation of derivatized mannitol and trehalose with methadone, naltrexone or insulin as the model drugs by contacting the alcogels with a solution of the drug before the supercritical drying
step [100]. The resulting powder was found to have a very low density which in turn could enable its application as an aerosol for inhalation. The authors claimed that the aerogel powder containing therapeutic agent had particle size in the range of 0.5 to 10 μm as a result of a milling process which would permit them to reach the alveoli of a human subject’s lungs upon inhalation.

Biodegradable starch is an abundant, edible, nontoxic and low cost polysaccharide which is composed mainly of amyllose and amylpectin, the relative proportions of which are dependent upon the starch source [26]. In synthesis of starch aerogels, the first step is to swell the starch by placing it in an aqueous solution [26]. While heating, the starch dissolves and gelation occurs with the destruction of granular structure. Upon cooling and aging, starch hydrogel is formed following the partial reorganization and the crystallization of the polysaccharide structure. The hydrogel is then subjected to solvent exchange with an alcohol followed by supercritical drying resulting in a starch aerogel. The amylose amount and the temperature at which gelation occurs are parameters governing the hydrogel and thus the aerogel structure.

Mehling et al. loaded paracetamol and ibuprofen as model drugs on starch aerogels and investigated their release in 0.2 M phosphate buffer at a pH of 7.2 and at 37 °C [53]. Different kinds of starch, potato starch and modified starch (Eurylon 7) were used to prepare starch aerogels. Owing to the high solubility of paracetamol in ethanol, the loading was performed during the solvent exchange step and loadings as high as 25% by weight was obtained. SEM images of those aerogels which are drug loaded and drug free are given in Fig. 9. The average pore size of the potato starch aerogel (around 7.2 nm) was higher than that of the Eurylon 7 (around 1.9 nm) based aerogel. SEM image of the paracetamol loaded potato starch aerogel indicates the presence of some paracetamol in crystalline form due to the possible crystallization of paracetamol inside the pores during the supercritical drying step as explained previously. On the other hand, ibuprofen which was loaded by adsorption from a solution of scCO2 was found to be in amorphous form. Similar amounts of loading could be achieved for both drugs using the two methods. The specific surface area and the pore size were seen as the major factors affecting the loading. Higher surface areas resulted in higher drug loading. Furthermore, smaller pore sizes led to increased loading due to capillary forces holding the drug molecules inside. It was shown that the release kinetics were dependent on the structure of the matrix along with the properties of the model drugs. Since paracetamol was highly soluble at given pH, its dissolution was faster than ibuprofen for all matrices. However, the release rate of ibuprofen which was adsorbed from scCO2 and had a lower solubility than paracetamol was highly dependent on the kind of matrix. The rate was higher with fast collapsing matrices such as Eurylon 7 and hydrophilic silica aerogel and lower with more stable matrices such as potato starch aerogel.

The loading capacity of corn starch aerogel microspheres was investigated using the model drug ketoprofen and the loading capacity of these organic aerogels with surface areas ranging from 34 m2/g to 120 m2/g was found to be in the same range of silica aerogels with higher surface areas (around 1000 m2/g) [31]. The loading was given as $1.1 \times 10^{-3}$ g/m² corresponding to 15.8% by weight [31] compared to the loading in the silica aerogel matrix which was reported as 2.8–3.8 $\times 10^{-4}$ g/m² corresponding to around 30% by weight [55]. The effect of the oil to starch ratio, surfactant amount and the gelation temperature on the physical properties of the starch aerogels was also investigated. The maximum loading capacity was found to be dependent on the density, the surface area and the pore size. Lower densities with high porosities and high surface areas were shown to enhance the loading of the active compound.

The importance of the operating conditions of the supercritical drying process on the physical properties such as density, surface area and pore size was demonstrated in a very recent study on starch aerogel microspheres [101]. It was shown that long drying times were detrimental in preserving the porosity of starch aerogels. This was attributed to the local distortions and collapses in the aerogel structure by extraction of structural water from the starch aerogel network by scCO2 [102]. Microspheres prepared using a shorter supercritical drying period had desirable properties. The time dependent loading of the ketoprofen on starch aerogels resulted in a specific loading capacity of almost one order of magnitude higher than that obtained for silica aerogels as a matrix [55,101]. The release of the ketoprofen was shown to follow the Korsmeyer–Peppas release model involving both the diffusion of the active ingredient and the matrix erosion processes [101].

Another polysaccharide, alginate, was also used to prepare aerogels which were then investigated as drug delivery vehicles. Alginate which is an abundant polysaccharide is used as a host material for several biologically active materials in various applications [103,104]. The chemical structure of alginate consists of a copolymer of 1,4-linked-β-D-mannuronic acid (M) and α-L-guluronic acid (G) [103–105]. Divalent cations such as Ca2+ are usually used to trigger the gelation of the alginate following the “egg-box” gelation model mechanism [33]. The addition of the alginate solution to the cation source solution (diffusion method) [106] or the controlled addition of the cation (the cross-linking ion) to the polysaccharide solution (internal setting method) [107] can induce the gelation of the alginate.

Mehling et al. prepared Na-alginate aerogels and loaded them with ibuprofen with the post-treatment method [53]. It was observed that the release of the drug from alginate aerogels was quite fast due to the high affinity of alginate for water and more efficient transport of the drug to the surrounding medium due to the large pores of the aerogel with an average pore radius around 11.7 nm. In another study concerning alginate aerogels, the effect of preparation conditions on the properties of the aerogels and on the release of a model drug, nicotinic acid was investigated [62]. It was shown that the initial alginate concentration enabled control over the drug release. Increasing the alginate concentration resulted in more compact aerogels with a
higher degree of cross-linking retarding the release of the drug. More compact structures exhibited less shrinkage and thus higher pore volumes. Furthermore, it was also observed that loading of the drug during the gel synthesis decreased shrinkage of the gels during the solvent exchange step.

Monodisperse alginate particles with a porous structure were synthesized using a prilling process [63]. An alginate solution containing ketoprofen as the model drug was sprayed into an aqueous or ethanol-soluble CaCl2 gelling bath through a nozzle. The resulting alginate beads were either supercritically or air/oven dried. Since the loading of the drug was performed prior to drying, the loadings of drugs that are soluble in scCO2 were lower compared to air dried samples due to extraction of the drug by scCO2 during drying. The porous structure resulting from scCO2 drying enhanced the dissolution of the drug and also allowed the modulation of the release rate of the drug. It was shown that performing the cross-linking in aqueous CaCl2 solutions resulted in the amorphous form of the drug compared to crystal clusters of ketoprofen obtained when the cross-linking was performed in ethanol.

Cellulose aerogels which are another type of organic aerogels are prepared either by freeze or supercritical drying of dissolved cellulose nanofibrils and nanowhiskers [15,108,109]. They have very similar properties compared to silica and other organic aerogels [65]. In addition to plant cellulose, bacterial cellulose is another interesting source due to its high purity, molecular weight, fiber strength and degree of hydration and has already a 3D framework [110]. Ultra-lightweight cellulose aerogels were prepared from purified bacterial cellulose as the starting material which was produced by the gram-negative bacterium Gluconacetobacter xylinum. The cultivated bacterial cellulose was briefly boiled, treated with NaOH and then washed with deionized water for neutralization. Resulting hydrogels were also subjected to solvent exchange step prior drying. The use of supercritical drying conserved the dimensional stability of the materials leading to very small amounts of shrinkage [110]. Haimer et al. studied the loading of dexamethasone and L-ascorbic acid on bacterial cellulose matrices via precipitation from ethanolic solutions by supercritical carbon dioxide [65]. It was shown that the drug loading was independent of the nature of the drug contrary to the release profile which was dependent on the type of the loaded substance. The release rate was also shown to be dependent on the thickness of the bacterial cellulose matrix due to the fact that the release was found to be driven by diffusion only. The release kinetics could be successfully predicted using a mathematical model taking into account both the solvent diffusion into the pores and the solute diffusion out of the pores. Successful predictions confirmed that no specific interaction existed between the drugs and cellulose matrix.

Betz et al. prepared a novel whey protein-based aerogel for drug delivery applications [66]. Previously, it had been shown that water insoluble whey based hydrogels were suitable for the encapsulation of drugs [111,112]. The use of supercritical drying rather than freeze drying as the final step in the preparation of these materials resulted in the formation of biopolymer based aerogel structures. The covalent disulfide bonds within these materials prevented the collapse of the aerogel structure when placed in aqueous media and led to a pH dependent swelling behavior upon rehydration. The release of the drug depending mostly on its diffusivity indicated a promising potential for the use of these materials in the drug delivery field. As shown in Fig. 10, the release of ketoprofen was retarded when it was encapsulated in aerogels compared to its pure form. The higher dissolution rate of ketoprofen at pH 6.8 was attributed to its higher solubility at neutral pH conditions.

6. Layered aerogels as drug delivery systems

Our immune system is ready to attack any unknown substance which is introduced into the body, thus the designed drug delivery vehicles should have their own protective layer or they should mimic already recognized substances. In addition, the application of some systems like hydrophilic aerogels which collapse when placed in aqueous solutions can be extended by covering them with protective layers. These layers may not only protect the core material but also regulate the release of the drug which is a desirable aspect in drug delivery applications. It was shown that such stealth properties can be incorporated to nanstructured drug carriers by proper design of the density, thickness and hydrophilicity of the coatings [113]. For example, Chen et al. prepared an armor from poly(butyl methacrylate) latex particles around polymer vesicles which were prepared from poly(n-butyl methacrylate)-b-(N,N-dimethylaminoethyl methacrylate) block copolymers which could enable the control of the overall rigidity of the polymer vesicles [114]. In addition, it was proposed that this armor could be an effective tool to vary the permeability and thus control the release of the drugs. The polymer vesicles were also coated with a stealth supracolloidal armor which was prepared from a mixture of ethyl acrylate and methacrylic acid. The partial dissolution of this armor upon pH change could be exploited for drug delivery. The same strategy could also be applied to suitable aerogel systems to provide protection and also a controlled release.

Another advantage of using a multi-layered system could be to obtain a sequential release of different drugs for combined therapeutic effect [115]. The loading of two or more different drugs on different layers can also prevent the encounter of these drugs which lose their effectiveness when they interact. The design of multi-layers with different hydrophilicity levels could provide a controlled and prolonged release of a drug with subsequent collapse of successive layers and also control of the diffusion through the layers. The use of hydrophilic core with a hydrophobic coating, vice versa, or combining hydrophilic and hydrophobic cores in the same device could enable the delivery of hydrophilic and hydrophobic drugs by the same drug delivery vehicle [116]. Furthermore, stimuli sensitive layers might lead to target specific delivery, enabling release of different drugs at different physiological conditions [117]. For example, different layers could be designed such that each layer would be sensitive to a different pH value. Thus, this layered system could release different drugs at different pH conditions in the body.

Different methods are already established to design layered materials. Suitable techniques which should neither damage nor collapse the porous structure have to be developed not to affect the high pore volumes and surface areas of porous aerogels. Layer by layer (LbL) assembly technique involving the deposition of positively and negatively charged species is a common method which is also applied to coat diverse biomedically relevant substrates [118]. The ability of achieving high drug loading within the film layer and conformal coating complex geometries with micro- to nanometer scales are attracting features of
Aerogel based systems constitute an emerging platform for drug delivery. The studies carried out so far show that aerogel based materials are promising due to their high drug loading capacities, their ability for controlled drug release, their capability to increase the bioavailability of low solubility drugs, and to improve both their stability and their release kinetics. Not only their unique properties, such as very high porosities and high surface areas, but also the flexibility of sol–gel chemistry plays an important role [15]. The changes in pore volume and/or surface area of the aerogels as well as their surface chemistry, which can be manipulated by different surface functionalization techniques, were shown to affect the adsorption and release of the drugs. Furthermore, composite and layered aerogels provide new possibilities to achieve the targeted formulation properties.

Along with the increasing interest and research on these nanostructured materials as drug delivery vehicles, there exist several challenges for commercialization. For example, studies on toxicity and biocompatibility of aerogels are very rare. Such tests should accompany the studies in this area and the synthesized materials at each of the preparation steps should be tested to confirm their suitability in the drug delivery field. The interactions between the drugs and the aerogel matrices should be deeply investigated in order to control the drug loadings, release rates and also to prevent any undesired reactions. Moreover, alternative functionalization or coating methods need to be developed to protect the aerogels for long term use and increase their stability as well. New multi-layered materials should be designed to improve the

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![Fig. 11. The procedure for the preparation of PEG hydrogel coated silica aerogels. Adapted from [60].](image-url)

![Fig. 12. The release kinetics of nicotinic acid from spherical multilayer alginate aerogels with different number of layers. Reprinted from [64] with permission from Elsevier.](image-url)
current aerogel systems and to develop new ways of controlled release with different number of layers. Furthermore, the preparation of hybrid aerogels comprising inorganic and organic components can increase the performance of these materials in drug delivery applications. Coupling the high surface area of the inorganic components with biodegradable organic constituents may lead to novel materials with interesting properties. In light of this approach, Ayers et al. conducted a study investigating the preparation of silica chitosan aerogel composites and proposed that these materials could be used in different applications like drug delivery [120].

Another area which has hardly been investigated in drug delivery studies on aerogels is the mathematical modeling of drug loading and release processes. The developed models should take into account processes such as physical and chemical adsorption, diffusion inside the pores, crystallization occurring inside the nano-sized pores as well as on the external surface. These models should also incorporate matrix erosion processes. Such mathematical models will surely help to guide future studies and facilitate the commercialization of these materials.

Overall, the results of the studies summarized in this review show that both inorganic and organic aerogels present a huge potential in the field of drug delivery. Depending on the structural properties, the intended adsorption or release of the active ingredients can be obtained by tailoring the synthesis conditions. Taking into account the increasing importance of aerogels in a variety of application areas, their use in drug delivery can be expected to grow in the coming years.

References


